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United States Patent [19]**Bergström et al.**[11] **Patent Number:** **5,739,407**[45] **Date of Patent:** **Apr. 14, 1998**[54] **HUMAN β -CASEIN, PROCESS FOR PRODUCING IT AND USE THEREOF**

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[56] **References Cited****FOREIGN PATENT DOCUMENTS**

0247494	12/1987	European Pat. Off. .
0264166	4/1988	European Pat. Off. .
0279582	8/1988	European Pat. Off. .
8204443	12/1982	WIPO .
8800239	1/1988	WIPO .
8801648	3/1988	WIPO .
9103551	3/1991	WIPO .
9108216	6/1991	WIPO .
9108675	6/1991	WIPO .
9203917	3/1992	WIPO .

OTHER PUBLICATIONS

J Van Brunt (1988) *Bio/Technology* 6:1149-1154.

MR Capecchi (1989) *Science* 244:1288-1292.

TA Brown (1990) *Gene Cloning*, pp. 153-177.

K-F Lee et al (1989) *Mol Cell Biol* 9:560-565.

American Academy of Pediatrics, Committee on Nutrition: "Commentary on Breast-Feeding and Infant Formulas, including Proposed Standards for Formulas"; *Pediatrics* 57, 278-285 (1976).

American Academy of Pediatrics, Committee on Nutrition: "Soy-Protein: Recommendations for Use in Infant Feeding"; *Pediatrics*, vol. 72, No. 3, pp. 359-363 (1983).

J. Bonsing et al, "Complete Nucleotide Sequence of the Bovine Beta-Casein Gene"; *Aust. J. Biol. Sci.*, vol. 41, pp. 527-537 (1988).

(List continued on next page.)

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[57] **ABSTRACT**

The present invention relates to a DNA sequence encoding the human milk protein β -casein or an analogue or variant thereof which has either the calcium binding activity of human β -casein, or opioid activity, or angiotensin converting enzyme (ACE) inhibitory activity, or a combination of any two or three of these activities. The DNA sequence may optionally contain one or more intron sequences and permissive RNA splice signals. The DNA sequence is used in the production of recombinant human β -casein, advantageously by means of production in transgenic non-human mammals such as bovine species. In one embodiment, the DNA sequence is inserted into a milk protein gene of a mammal such as a whey acidic protein (WAP) gene. The main use of the recombinant human β -casein is as a constituent of infant formulae. It is contemplated that the recombinant human β -casein provides a substantial improvement of the nutritional and biological value of the formulae in that a closer similarity to human milk is obtained.

7 Claims, 26 Drawing Sheets